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Managing lorlatinib together: An overview and practical guide for patients by *ALK*-positive NSCLC patients and medical experts

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ABSTRACT

Lorlatinib is an oral treatment for patients with advanced *ALK*-positive non-small cell lung cancer (NSCLC). Its efficacy was demonstrated in the CROWN clinical study, in which data from 5 years of follow-up demonstrated effective long-term disease control in patients with advanced *ALK*-positive NSCLC. While lorlatinib has a distinct side effect profile, its side effects are generally manageable. Managing side effects successfully is critical to preserving patient quality of life and promoting adherence to treatment—both of which are key to maximizing the long-term benefits of lorlatinib. The CROWN study showed that lorlatinib-associated side effects can be managed with dose adjustments, such as lowering the daily dose, without sacrificing treatment effectiveness. This guide, developed collaboratively by patients living with advanced *ALK*-positive NSCLC and healthcare professionals experienced with managing lorlatinib treatment, aims to help patients understand what to expect from treatment and how to take an informed, active role in their care.

1. Background

Lung cancer is the most diagnosed cancer worldwide, with nearly 2.5 million new cases annually [1]. Approximately 85% of lung cancer diagnoses are the non-small cell lung cancer (NSCLC) subtype [2]. Several biological hallmarks (biomarkers) of cancer, such as abnormal alterations or errors in genes (DNA mutations), have been discovered that enhance the growth and spread of NSCLC [3]. These biomarkers have been shown to impact anticipated health outcomes (prognosis). Treatments have been developed to effectively treat these NSCLC subtypes by targeting the

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; ESMO, European Society for Medical Oncology; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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corresponding biomarkers [4–6]. Additional information about biomarkers can be found in Appendix A1.

One known biomarker is a gene called anaplastic lymphoma kinase (*ALK*). Changes in the *ALK* gene occur in about 2% to 7% of NSCLC cases. These cases are called *ALK*-positive NSCLC [7,8]. The *ALK* gene makes a protein called ALK that controls how cells grow. Changes to the *ALK* gene result in the ALK protein working improperly, which enables cancer cells to grow uncontrollably [9]. *ALK*-positive NSCLC is often diagnosed at a late stage, meaning the cancer may have already spread to other parts of the body (metastasized), often to the brain and/or spinal cord (also known as the central nervous system, or CNS) [6,10–12]. *ALK*-positive NSCLC can present as an aggressive form of cancer that can severely impact the patient's quality of life [11,13,14]. Patients may experience a large number of symptoms, or sometimes severe symptoms, that impact their daily life and ability to work.

ALK-positive NSCLC can improve or be controlled with oral medications called ALK tyrosine kinase inhibitors (TKIs), which fall into a type of treatments known as targeted therapy [15–18]. ALK TKIs target and block activity of the ALK protein, which can slow or stop the growth of cancer cells [19]. Current international treatment guidelines, such as European Society for Medical Oncology (ESMO), recommend treating *ALK*-positive NSCLC with an ALK TKI (for example, the second-generation ALK TKIs alectinib or brigatinib or the newer third-generation ALK TKI lorlatinib) [4,20]. These treatment recommendation guidelines are based on clinical studies that evaluated how long the medications were able to control cancer growth and spread (known as progression-free survival in clinical trials), with special interest in their effectiveness in controlling or preventing cancer in the brain and/or spinal cord (CNS) [4,15–17,20]. Increasing how long the medication is able to control cancer growth and spread and how long the patient lives after starting the medication (known as overall survival in clinical studies) are commonly cited as important factors influencing treatment choice for NSCLC [21,22].

Lorlatinib is a newer ALK TKI that has demonstrated compelling clinical efficacy in controlling *ALK*-positive NSCLC disease [15,23–26]. In a phase 3 clinical study called CROWN, 149 patients with *ALK*-positive NSCLC took lorlatinib as their first cancer treatment. As a phase 3 study, CROWN compared lorlatinib to a first-generation ALK TKI called crizotinib to confirm its efficacy and safety in a broad application [15,25,26]. Here, we focus on lorlatinib. Lorlatinib demonstrated the ability to prevent the development of new brain metastases in most patients and effectively manage existing brain disease, while associated with tolerable and manageable side effects [15,25,26]. At the 5-year treatment follow-up mark, the study reported that about 6 out of every 10 (60%) patients who took lorlatinib were alive without their cancer getting worse [25]. Moreover, most patients (about 9 out of every 10, or 92%) who took lorlatinib had no signs of cancer spreading to or advancing in their brain. In another study, lorlatinib was tested in patients with *ALK*-positive NSCLC who had already tried at least one other ALK TKI treatment before using lorlatinib [23,24,27]. The findings from these clinical studies are now used by the healthcare team when deciding the best treatment to recommend for patients.

For patients with *ALK*-positive NSCLC, their journey from diagnosis through treatment may be overwhelming. Appendix Fig. A1 diagrams a typical journey, although it is not reflective of all patients. This process can also be full of complex terminology, and Appendix Table A1 provides definitions of common terms a patient may encounter on their journey. The focus of this publication is to provide guidance and support to patients and their care partners as they navigate the treatment journey on lorlatinib. Additional guidance for understanding the diagnosis portion of the journey and suggested questions to ask the healthcare team can be found in Appendix Fig. A2.

Feeling unwell due to side effects caused by cancer treatment is common and can be expected; combined, the cancer and its treatment's side effects can negatively impact quality of life [28,29]. Persevering through side effects due to cancer treatment without speaking with the healthcare team can unintentionally lead to needing to stop treatment early, which could prevent a patient from getting the maximum potential benefit from the medicine. Regularly checking for side effects is necessary for any cancer treatment to ensure it is suitable and effective for the patient [29]. By drawing from the experiences of patients with *ALK*-positive NSCLC and the expertise of clinical specialists, the goal of this guide is to encourage proactive reporting and management of side effects to ensure patients can safely continue using lorlatinib to treat their cancer, for as long as they derive benefit from the treatment. This guide is intended to support, but not replace, individualized, trust-based discussions with the healthcare team. Decisions about treatment should always be made in partnership with healthcare providers, while considering each patient's unique needs and circumstances, including the patient's overall health and well-being.

2. Patient experience and preferences are individualized

Open communication between the patient, care partners, and healthcare team is important [30,31]. While the healthcare team will typically guide treatment selection based on clinical expertise, it is important for patients to communicate how they are tolerating side effects and to share any concerns, as experiences and needs can vary widely between individuals. Fig. 1 includes a list of questions, based on patients' experiences, that patients should consider when preparing for visits or conversations with their healthcare team.

A recent study surveyed patients with *ALK*-positive NSCLC and oncologists experienced in treating this disease, to identify which aspect of treatment they consider most important [32]. While both groups agreed that the effectiveness of the medication was essential, there were clear differences in treatment priorities. Patients emphasized controlling or preventing cancer in the brain, even if it meant an increased chance of experiencing side effects. In contrast, oncologists focused on extending the time patients live without their cancer worsening. The willingness to tolerate side effects varied between the two groups, highlighting the need for effective communication between patients and their healthcare providers to ensure treatment decisions align with individual priorities and concerns [32].

Understanding the trade-offs between treatment effectiveness and potential side effects that both patients and oncologists are willing to make can enhance shared decision-making and treatment adherence [29,33,34]. Treatment management decisions can then be individualized based on each patient's expectations and tolerance.

3. General side effect management

Cancer treatments often come with side effects, some of which can be quite bothersome and require careful monitoring and management (with what is referred to as clinical interventions) [28,29]. Management recommendations for lorlatinib side effects are detailed in many publications, guidelines, and podcasts for healthcare providers [30,31,35–40]. A group of oncology experts specializing in lorlatinib developed a guide for healthcare providers that combines insights from clinical studies and real-world experiences to help manage the side effects of lorlatinib [31]. The goal is to ensure continuous treatment by proactively addressing side effects, minimizing their impact on the patient and their quality of life during therapy. The guide includes steps to (1) prepare patients and care partners for potential side effects, (2) monitor for and report side effects, (3) manage side effects promptly, and (4) reassess side effects continuously (Fig. 2).

The preparation informs patients and their care partners about lorlatinib treatment, detailing potential side effects, their likelihood, and typical timeline as reported in studies [31]. Patients should consult their healthcare team for expert advice and management strategies. Starting with the initial dose, lorlatinib's regimen may be personalized based on the patient's clinical history [31]. Healthcare professionals may manage side effects with temporary treatment breaks or lorlatinib dose

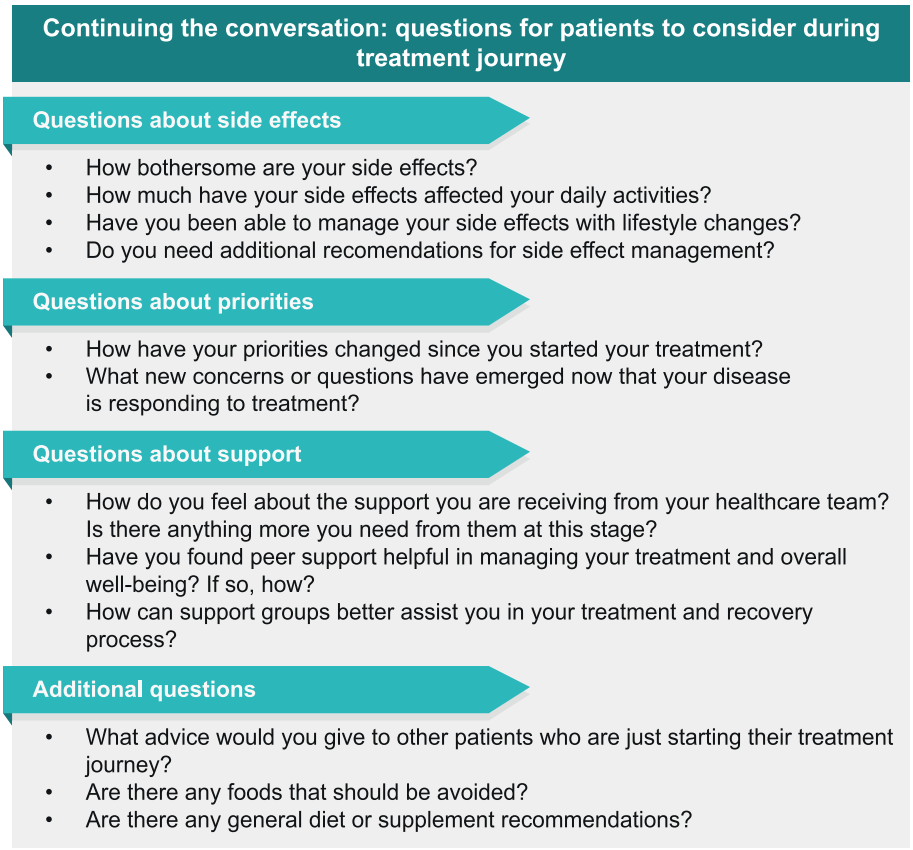

Fig. 1. Continuing the conversation between patients and their healthcare providers. Questions for patients to consider during treatment.

reductions in 25-mg increments. It is important to note that in the CROWN study, when the lorlatinib dose was lowered from the starting dose of 100 mg down to 75 mg to manage side effects, there was no negative impact on the drug's effectiveness [25,31]. Some patients can expect dose adjustments during treatment, with healthcare teams closely monitoring their cancer to ensure continued benefit and disease control. The goal is to tailor lorlatinib based on each patient's treatment expectation, tolerance, and how bothersome they find side effects. Not all side effects require dose changes; alternative strategies can include those requiring medication (pharmacological) and those that require no additional medication (non-pharmacological), and these strategies may be used before, instead of, or along with dose adjustments [31]. Proactive communication between patients and their healthcare team is crucial to preserve quality of life [31,39], which is an important factor as patients may be on lorlatinib for years.

After starting lorlatinib treatment, patients should expect regular monitoring for the presence and severity of side effects [31]. It is important that patients and their care partners report any side effects to their healthcare team as they occur, rather than waiting to be asked during scheduled visits or phone calls. Keeping a diary to comprehensively document side effect experiences may support more accurate and timely communication with the healthcare team. Fig. 3 provides a list of questions patients may be asked by their healthcare team. It is recommended that patients prepare for each visit by noting any new or worsening side effects since their last appointment, along with any questions they have. The healthcare team will inquire how bothersome the side effects are to the patient, which will influence management decisions [31]. Effective side effect management requires collaboration between patients, care partners, and healthcare professionals to find the best strategy for preserving quality of life while maintaining treatment effectiveness. Proactive and honest communication is essential and serves as the cornerstone of managing side effects, which is an ongoing part of the treatment journey.

4. Overview of side effects associated with lorlatinib

In the CROWN study, as expected, nearly all patients who received either lorlatinib (the treatment being investigated) or crizotinib (the reference treatment) reported that they had at least one side effect of any severity during treatment [15,25,26]. After 5 years of follow-up, with proper side effect management—including treatment breaks and lowering lorlatinib dose—only 8 of the 149 patients in the CROWN study (5%) permanently stopped lorlatinib due to side effects considered related to lorlatinib; a similar discontinuation rate was observed with crizotinib, with 8 patients (6%) permanently stopping treatment [25,41].

Lorlatinib has a unique side effect profile compared with other ALK TKIs [30]; a patient-friendly timeline of side effects related to lorlatinib has been developed (Fig. 4**)**. This timeline provides an estimate of the likelihood of each side effect occurring, based on data from lorlatinib clinical studies including CROWN [31,41]. Symptomatic side effects like limb swelling (edema), weight gain, numbness or tingling (neuropathy), and mild changes in mood, speech, thinking, or behavior can occur and are deemed typically treatable and improvable in most cases, meaning most people can continue taking lorlatinib without having to stop [31,30]. The general recommendations for management of side effects are shown in Fig. 5**.**

Additionally, lorlatinib is associated with changes in laboratory test results that aren't associated with symptoms, particularly ones related to increased blood lipid levels (hyperlipidemia) [31,30]. In the CROWN study, increased blood lipid levels were reported as high cholesterol in 72% of patients and as high triglycerides in 66% of patients [25]. As the average onset of hyperlipidemia was early, at 0.5 months [41], regular blood tests before and during treatment are essential for monitoring

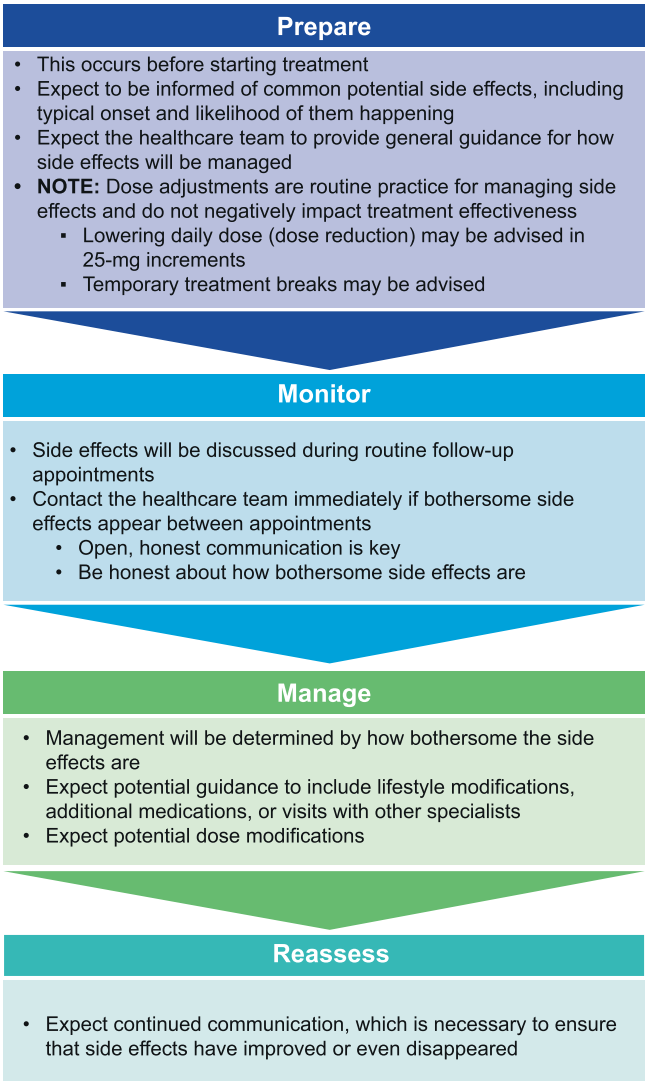

Fig. 2. General outline[a] of side effect management. [a]Outline follows the strategy described in Liu G, et al. (2024) [31].

these levels [31]. Common management strategies include using lipid-lowering medications, such as statins, and lifestyle modifications, such as dietary changes [30,31]. Patients should expect to work closely with their healthcare team to find the best management strategy for them; this may require additional medications or switching statins [30,31]. Following management in the CROWN study, most hyperlipidemia events (73%) improved or were completely resolved (lipid levels were brought back to normal levels with management strategies) [42]. Additionally, the high rate of hyperlipidemia has not been associated with an increased likelihood of side effects affecting the heart or blood vessels (cardiovascular) so far [25]. It is important for patients to inform all members of their healthcare team of their complete list of medications and supplements, as patients may work with their primary care physician or be referred to a specialist (for example, a cardiologist) to manage their side effects, and not all statins are compatible with lorlatinib [31,35].

Swelling (edema) is defined as excess fluid accumulation in body tissues; this can be more prominent in the hands and feet (upper and lower extremities) [35]. In the CROWN study, swelling occurred in more than half of the patients taking lorlatinib (57%), with symptoms first appearing on average around 1.8 months on treatment [25,41]. Most cases were mild or moderate, with only 4% of patients reporting severe swelling [25]. Consulting with the healthcare team can help determine the best management regimen, as shown in Fig. 5**A.**

Increased body weight, or weight gain, occurred in less than half of patients (44%) in the CROWN study, with average time to onset of 3.7 months [25,41]. About half of patients with weight gain (23% of total patients in CROWN study) reported severe weight gain, defined as an at least 20% increase in body weight over baseline (pre-cancer diagnosis weight) [25,43]. Edema, as described earlier, may contribute to noticeable weight gain [31]; 4 of 10 patients (40%) who reported weight gain and/or edema in the CROWN study reported experiencing both [42]. Weight gain should be discussed with the healthcare team to ensure proper management strategies, such as healthy nutrition, exercise, and other interventions, are implemented to preserve quality of life (Fig. 5**A**) [30,31].

Tingling and/or numbness, or peripheral neuropathy, is a condition that occurs when nerves in the hands, feet, or other areas of the body are sensitized, causing sensations like pain, numbness, tingling, or muscle weakness [30,31]. Peripheral neuropathy was reported in 44% of patients in the CROWN study, with only 2 of the 149 patients (1%) reporting severe cases [25]. On average, symptoms of peripheral neuropathy began around 3.7 months [41]. Peripheral neuropathy is typically reversible following dose adjustments [31], which are included in the management strategies outlined in Fig. 5**A**.

In the CROWN study, changes in mood, speech, behavior, or thinking were grouped under a broad term of CNS side effects, and in most cases they were not permanent [25,30,31]. From a patient perspective, it is important to discuss the individual categories of CNS side effects (for example, mood, speech, behavior, thinking) based on their presentation, which will help patients and care partners to recognize them. Generally, these side effects are managed with a temporary treatment break (about 1–2 weeks) [31]. Symptoms should generally improve and, once cleared by the healthcare team, patients may be advised to restart lorlatinib at a reduced dose (starting dose minus 25 mg) [31], as summarized in Fig. 5**B**. It is important to note that CNS side effects are reversible with proactive management [30,31], and in the CROWN study, only 3 of the 149 patients permanently stopped lorlatinib due to CNS side effects considered related to lorlatinib [25].

Memory issues and difficulty concentrating (cognitive effects) occurred in 28% of patients in the CROWN study, with mild or moderate presentation in most patients [25]; the average time to onset was 5.1 months [31]. Symptoms such as anxiety and depression (mood effects) occurred in 21% of patients, with only 2 patients (1%) reporting severe effects [25]; median time to onset was 1.2 months [31]. Speech effects, including slurred speech, occurred in 6% of patients, with mild to moderate presentation in all but 1 patient (1%) [25]; the average time to onset was 3.5 months [31]. Hallucinations (psychotic effects), which can present as an individual hearing, smelling, or seeing something that is not actually there, occurred in 5% of patients, with most patients reporting mild or moderate symptoms [25,44,45]. One of the 149 patients permanently stopped lorlatinib due to psychotic effects [25]; the average time to onset was 1.4 months [31].

After 5 years of following patients taking lorlatinib in the CROWN study, for each of the CNS side effect categories, the highest rate of new occurrences was in the first 6 months of treatment [41]. Clinical experts emphasize the importance of preparing patients and their care partners for potential CNS side effects before starting lorlatinib treatment [30,31]. By asking themselves simple questions (see Appendix Table A2), patients can help better describe any symptoms of common CNS side effects they may experience. Patients and care partners are encouraged to promptly report any symptoms or changes, even if not bothersome or minor, to their healthcare team to minimize the impact on their quality of life [31]. During planned follow-up appointments, patients should expect questions about side effects like memory loss, impaired judgment, and mood changes. Since these changes can sometimes be hard for patients to notice themselves, patient care partners can help in identifying these side effects, especially reporting any changes in the patient's personality or interactions with family and friends. It is

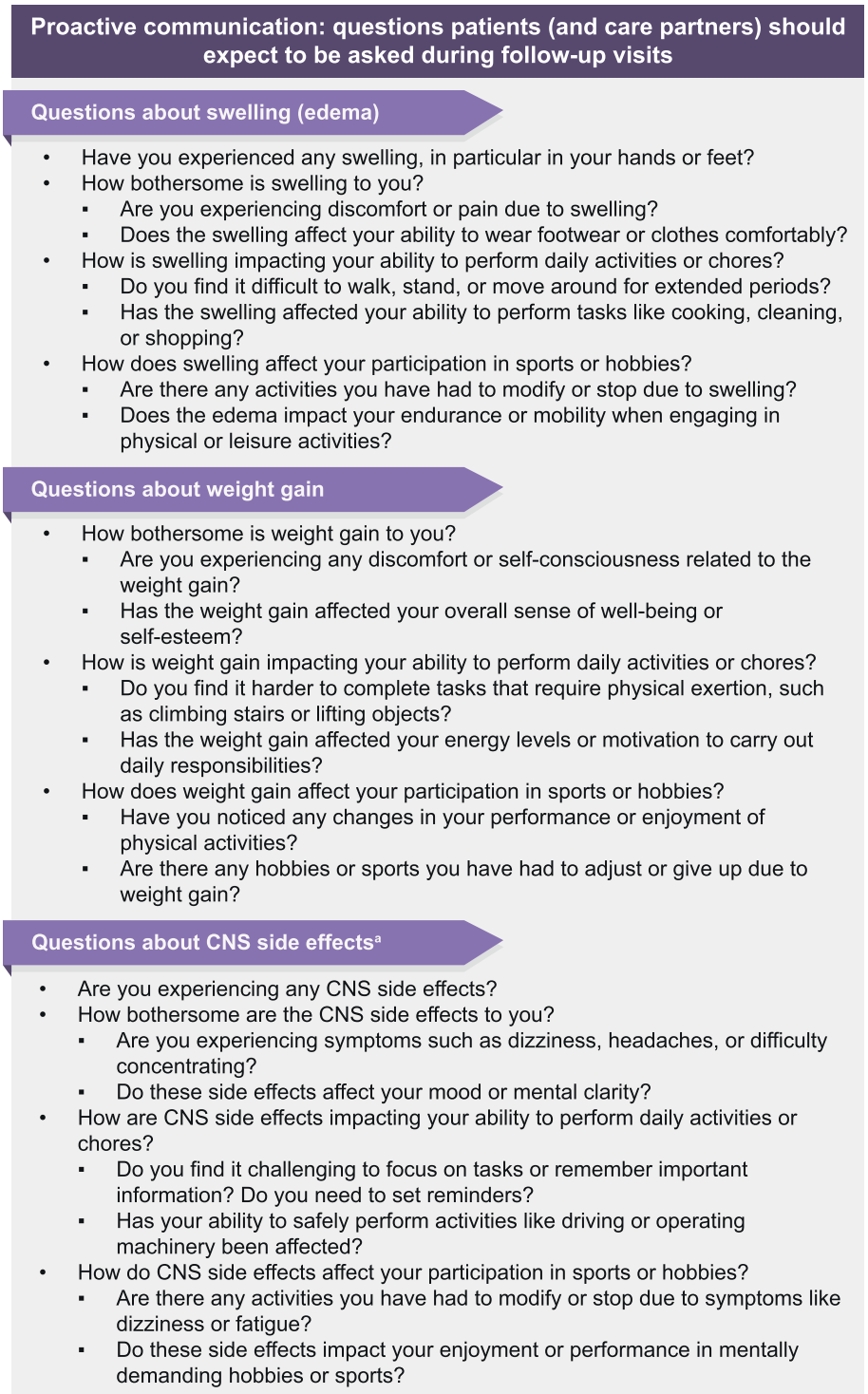

Fig. 3. Questions the healthcare team may ask patients and care partners during follow-up. CNS, central nervous system. [a]CNS side effects included a broad range of effects, such as changes in mood, speech, behavior, or thinking.

recommended that care partners accompany patients to appointments whenever possible to ensure these observations are communicated to the healthcare team.

In addition to the unique side effects associated with lorlatinib, patients may experience side effects that are also common with other ALK TKIs and cancer treatments, including fatigue and gastrointestinal distress, such as diarrhea and nausea [25,30]. Patients should report any side effects they experience while taking lorlatinib. Patients and their care partners will work with their healthcare team to ensure that side effects are managed or tolerable. To facilitate timely management, before beginning treatment, patients should become familiar with the process of how to report side effects. This includes identifying which member of their healthcare team should be contacted about side effects.

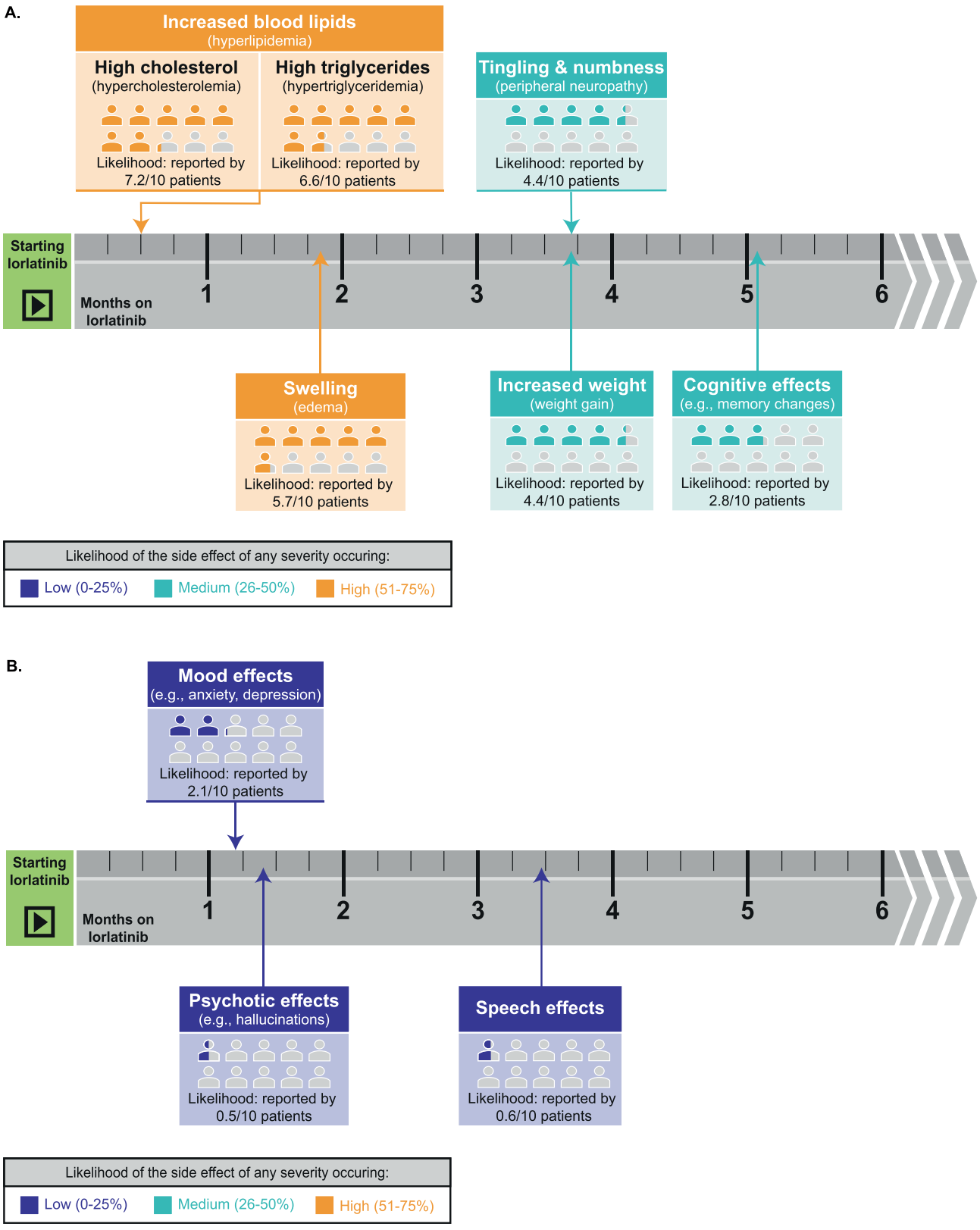

Fig. 4. Average onset and the likelihood of select lorlatinib-associated side effects [25,31,41]. These are average onset times, and side effects can appear at any time on lorlatinib treatment. A. Common side effects. B. Less common side effects. CNS, central nervous system.

5. Conclusion

This guide aims to prepare patients prescribed lorlatinib for the potential side effects and provides guidance on how to report them to their healthcare team. Healthcare experts should encourage patients to ask questions to help make more informed decisions during their cancer care. Since side effects can impact quality of life [29], patients should be well-informed about the type, likelihood, and timeline of potential side

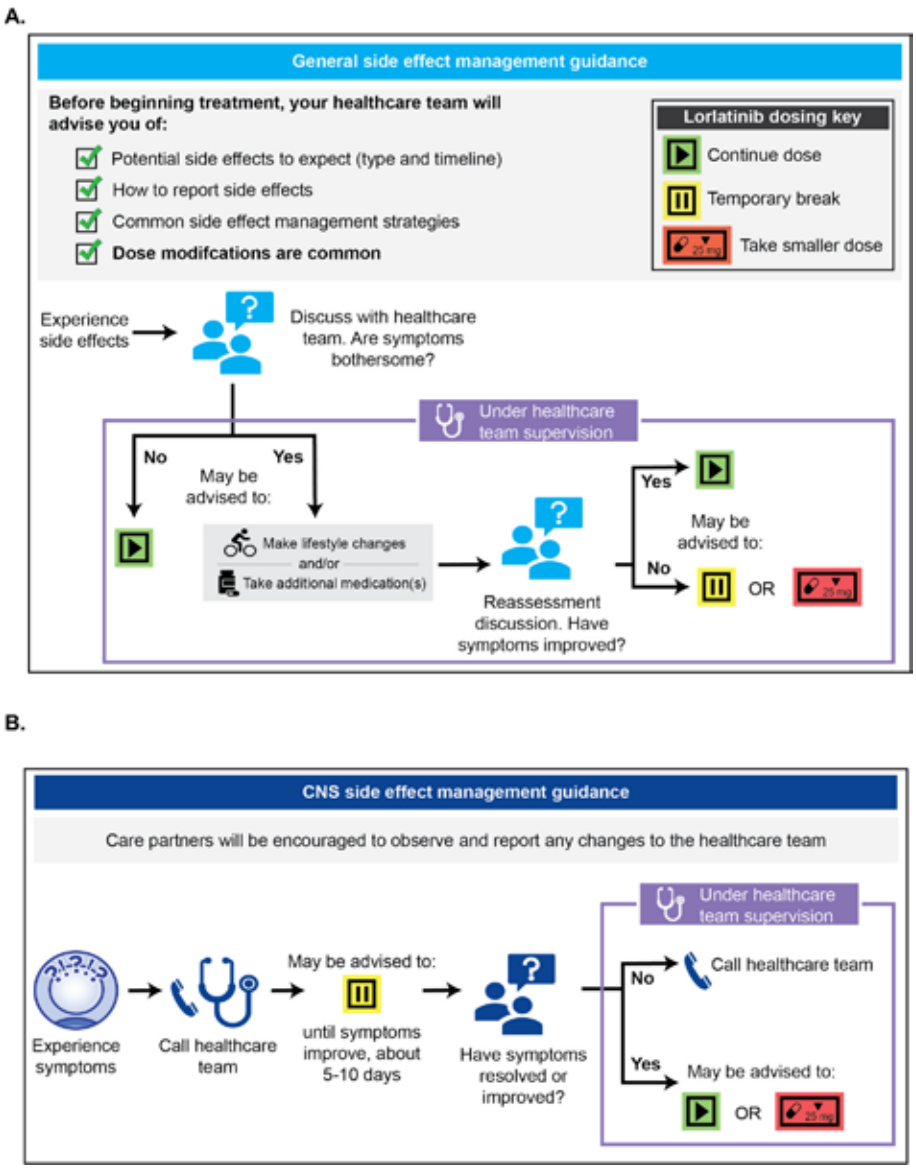

Fig. 5. General management recommendations for common side effects associated with lorlatinib.

effects associated with lorlatinib [31]. This knowledge enables early detection and timely management, minimizing the impact on daily life. While most management strategies involve lifestyle modifications or pharmacological approaches, a temporary treatment break and/or lowering of lorlatinib dose may sometimes be necessary. Clinical studies show that adjusting the lorlatinib dose can effectively manage side effects without compromising treatment benefits [25]. Through collaboration, patients, care partners, and healthcare professionals can maintain the patient's quality of life during lorlatinib treatment, ensuring continued benefits from this therapy.

CRediT authorship contribution statement

Nancee Pronsati: Writing – review & editing. **Geoffrey Liu:** Writing – review & editing. **Todd M. Bauer:** Writing – review & editing. **Enriqueta Felip:** Writing – review & editing. **Yasushi Goto:** Writing – review & editing. **Gerald Green:** Writing – review & editing. **Mary Grizzard:** Writing – review & editing. **Michael Hamel:** Writing – review & editing. **Julien Mazieres:** Writing – review & editing. **Tony Mok:** Writing – review & editing. **Stephanie Snow:** Writing – review & editing. **Benjamin J. Solomon:** Writing – review & editing. **Jan Stratmann:** Writing – review & editing. **Ken Culver:** Writing – review & editing.

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